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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,713	10/22/2003	Timothy C. Thompson	PRO025/4-9CON2US	9759

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VINSON & ELKINS, L.L.P.
1001 FANNIN STREET
2300 FIRST CITY TOWER
HOUSTON, TX 77002-6760

EXAMINER	
YAO, LEI	
ART UNIT	**PAPER NUMBER**
1642	

NOTIFICATION DATE	DELIVERY MODE
12/04/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

cporter@velaw.com
IPTLdocket@velaw.com
bmelder@velaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/690,713	THOMPSON, TIMOTHY C.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-31,33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-31,33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *p5, 10/22/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments and Amendment

The Amendment filed on 9/20/2007 in response to the previous Non-Final Office Action (5/17/2007) is acknowledged and has been entered.

Claims 1-25, 32, 34, 40-105 are cancelled.

Claims 26-31, 33, 35-39 are pending and are under consideration.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 10/22/2003 (page 5, MMM-BBBB) are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the **first paragraph of 35 U.S.C. 112:**

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-31, 33, and 35-39 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as stated below.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are drawn to a method for treating a subject having neoplastic disorder or disease of prostate comprising administering to the subject a composition comprising an anti-caveolin antibody wherein the antibody effective to inhibit metastasis in the neoplastic disorder. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provide an enabling disclosure of how to make and use a claimed invention. Thus, it would be expected that one of skill in the art would be able to treat a neoplastic disorder comprising prostate or breast cancer with any antibody to caveolin without undue experimentation by using the claimed method.

The specification teaches caveolin and expression of caveolin in human prostate cancers by immunoassay and correlation of caveolin expression and androgen sensitivity (page 34-36). However, the specification does not provide a method of treating prostate cancer or any neoplastic disorder by administering to the subject an anti-caveolin antibody. There are no working examples to guide to assist

the skilled artisan in practicing the claimed method of treating such neoplastic disorder comprising prostate disease with an antibody to caveolin.

The instant specification provides insufficient guidance or direction to predictably enable one of ordinary skill in the art to use the invention as claimed. Those of skill in the art recognize the unpredictability of treating tumors with antibodies. For example, Jain R. K. (Scientific American, 271(1): 58-65, July 1994) discloses the art known barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Dillman R. O., (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12): 41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Furthermore, as disclosed by Dillman, R. O. (Journal of Clinical Oncology, 12(7):1497-1515, 1994) discloses, after reviewing the literature on the use of unconjugated monoclonal antibodies to treat cancer, that "at present, there are no unconjugated monoclonal antibodies that have proven therapeutic benefit in hematologic malignancies or solid tumors." Thus, absent objective evidence to the contrary, it is highly unpredictable that applicant's unconjugated antibody would possess any therapeutic effects.

Moreover, the prior art does not provide convinced evidence that caveolin is directly related with tumorgenesis and is useful therapeutic target. For example, Nelson, J., teaches that progression of caveolin-depleted tumors is less than control tumors, but the tumor still progress, and that such therapy might be considered ineffective (Nelson, J. B. Nature Medicine, 4:1011-1012, 1998, page 1011, 3rd col). Additionally, the prior art has not settled the question of the biological function of caveolin in neoplastic disorder comprising prostate or breast cancer. For example, Lee et al., (Oncogene, vol 16, page 1391-1397, 1998) teach that caveolin expression is significantly reduced in human breast cancer cell compared with their normal mammary epithelial counter-parts (abstract, line 9-12).

No direction or guidance is provided in current specification to assist one skilled in the art using an antibody to caveolin in a method of treating neoplastic disorder comprising prostate or breast disease in a subject. In view of the lack of the predictability of the art to which the invention pertains as evidenced by the art of Jain R. K., Dillman R. O., Weiner, Dillman , Nelson, Lee et al., and the lack of established clinical protocols for effective immunotherapy, one skilled in the art would be forced into under experimentation in order to practice the claimed invention.

The response filed 9/20/2007 has been carefully considered but is deemed not to be persuasive.

At bridging page 5-6, applicant argues:

> The specification describes treating prostate cancer and metastatic prostate disorders by administering an anti-caveolin antibody, at least at paragraphs [0019] [0077] [0079] [0080] [0087] [0090] and [0095], all of which teach one of skill in the art that suppression of caveolin activity is useful in the treatment of metastatic prostate cancer and prostate noeplasia with potential to progress to become metastatic. Although the in vivo data was obtained by genetic suppression of caveolin, either by antisense or knockout constructs, one of skill in the art clearly understands that the suppression of caveolin activity can also be achieved by the use of antibody therapy as described.

In response, the Office agrees that the specification contemplates the method of treating prostate disorder by administering an anti-caveolin antibody, but no working example, treatment result, or sufficient guidance or direction was disclosed in the application. As discussed in the rejection, those skilled in the art recognize that treating tumors with antibodies is unpredictable and undue experimentation would be required before practice or use claimed invention for treating a patient. Using antisense or knockout constructs of caveolin only shows no or decreased expression of the caveolin protein in the transgenic mice, no correlation between the tumor suppression and absence of caveolin was demonstrated. Showing high levels of caveolin protein in metastatic prostate cancer tissue (table 1) only suggests the increased expression of caveolin protein as a result in the disease condition, does not demonstrate the abnormal expression contributing to the cancer development or tumorgenesis. Because the instant specification provides neither such teachings, nor objective evidence to support claimed method of inhibiting prostate cancer metastasis by administering an antibody to caveolin undue experimentation would be required before one skilled in the art practice claimed invention.

At page 6, applicant further argues inhibiting caveolin activity concurrently with androgen depletion therapy and states:

> It is an important aspect of the disclosure that inhibiting expression or activity of caveolin restores androgen sensitivity to prostate cancer. It is well known that prostate cancer is androgen dependent, or in other words, prostate cancer will not grow in the absence of androgen, and a primary treatment for prostate cancer includes androgen deprivation. Certain tumors, however, become androgen insensitive and no longer require androgen to grow. When this occurs, the tumor no longer responds to one of the most effective available treatment options. Restoring androgen sensitivity by concurrently suppressing caveolin and androgen is an important and novel contribution to the art. This effect and combination therapy are described in the Specification at least at paragraphs [0021] [0079] [0081] [0085] and [0117]. The treatment of prostate cancer by suppressing caveolin with an anticaveolin antibody in conjunction with reducing androgen levels, therefore, is fully enabled by the Specification.

In response, the androgen involved in prostate cancer and androgen therapy for prostate cancer are known in the art. However, instant claimed invention is drawn to a method of inhibiting metastasis with anti-caveolin antibody combined with androgen therapy, as discussed above applicant has not provided the enablement disclosure for the claimed method of treating prostate disorder using anti-caveolin antibody alone. The method claiming use of the same antibody in combination with androgen therapy for treating the same disease would have the same deficiency because if one skilled in the art does not know how to use one agent (anti-caveolin antibody) for treating the patient, one would certainly not know how to combine the same agent with another one for treating the same patient. In addition, one skilled in the art would expect an increased efficacy, additive or synergistic action, in the treatment when combined agents are used compared to any single one used. Since applicant has not shown the method of treating any metastatic prostate cancer comprising androgen insensitive or sensitive prostate disorder with caveolin antibody alone, one skilled in the art would not know how to use claimed method in combination.

At page 6, applicant further argue,

> it is known that anti-caveolin antibodies are available and a physician of skill in this art would require no undue experimentation to prepare and administer antibody therapy as described. It is further understood that treatment regimens and dosages for antibody therapies are known in the art and that specific treatments are determined in human clinical trials as approved by the FDA. Such human clinical trial data is not required for purposes of patentability.

In response, first, enablement rejection is based on that one skilled in the art does not know how to make or use claimed invention without quantity of undue experimentation. Knowing anti-caveolin antibodies available is far from enough to support the claimed method because one skilled in the art clearly know that not all the antibodies could be used for treating a disease associated with the abnormal expression or function of the antigen recognized by the antibody. Second, it should be clarified that the Office requires objective evidence, guideline/direction, or predictability, such as in vivo treatment of prostate disorder with the antibody, for claimed method, not human clinical trial data.

At page 7, applicant further states that the references relied on by the Action do not refute the enablement of applicant's asserted utility, and argues that the reference of Jain's does not discuss treating prostate disease and no caveolin, that the reference of Dillman's is too old when antibody

treatment is relatively new technology, and based on the references of Weiner's and more resent Dillman's inhibition of caveolin can be considered as biologic response for the treatment. In response, first, the rejection is pure enablement rejection under USC 112 first paragraph, not asserted utility of claimed method is questioned or rejected. Second, again as discussed in the rejection, each of the references points out the general problem of skilled in the art faced that is unpredictability of the treatment with biological agent, especially antibody, that is the reason that the objective evidence is necessary for an application claiming an invention of treating a disease with an antibody. Although treating a disease associated with the activity of an antigen by administering the antibody to the antigen is not new technology anymore, one skilled in the art still clearly know that not every available antibody is effective on treating a disease associated with the expression or activity of the antigen and not every disease could be treated with an antibody to the protein abnormally expressed in the disease condition without under experimentation and intensive in vivo research.

At page 8, applicant further argues the reference of Nelson provided in the rejection and states that the action appears to mischaracterize Nelson's, who states that prostate tumors are characterized by low rate of proliferation and apoptosis, therefore, any therapy that prolong survival serves consideration. In response, the Office agrees with the comments of Nelson on general prostate cancer treatment and therapy. However, Nelson does not suggest that antibody to caveolin is the way for such treatment because the mechanism of caveolin protein involved and its contribution to the prostate cancer development are not yet clearly defined and seem complicated with other proteins involved (col 2-3). Thus, treating prostate cancer with the antibody to caveolin would not be predictable and no guarantee to be successful. Thus, again, undue quantity of experimentations would be necessary before one skilled in the art could practice the claimed invention.

Applicant also submits web pages of clinically used Herceptin, an antibody to Her-2 protein, for the breast cancer treatment and states that one of skilled in the art thus understands that such antibodies can be used in the treatment of cancer and would include prostate cancer as stated in the application. In response, Herceptin is Her-2 antibody, which is used only for treating Her-2 expressed breast cancer because the expression and involvement of Her-2 protein in the breast cancer is clearly known and

intensive in vitro and in vivo research and experimentation had been done before using the antibody for the breast cancer treatment in clinic. However, in this case, as discussed above and stated in the Nelson's reference, the roles of caveolin protein in the prostate cancer condition are not clear currently. Showing high levels of caveolin protein in metastatic prostate cancer tissue only suggests the increased expression of caveolin protein as a result in the disease condition, does not demonstrate such abnormal expression contributing to the prostate cancer development or tumorgenesis. Therefore, administering caveolin antibody to a prostate cancer patient could inhibit the activity of the protein, which is not necessary or predicable to inhibit metastasis of the prostate cancer cell in the patients because no objective evidence, no guideline/direction, and no predictability have been provided in this application. Thus, applicant's arguments have not been found persuasive, and the rejection is maintained for reasons of the record.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Yang et al., (Clinical Cancer Research, vol 4, page 1873-1880, August, 1998)) disclose that elevated expression of caveolin is associated with prostate and breast cancer (entire paper). Yang et al., do not teach or suggest a method of treating any neoplastic disorder by administering to the subject a composition comprising an anti-caveolin antibody.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

LARRY R. HELMS, PH.D.
SUPERVISORY [illegible] EXAMINER